Synthesis of Functionalized 3-Pyridyl Methyl Ketones

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A synthesis of 3-pyridyl methyl ketones is described that employs a palladium-catalyzed olefination of 3-bromopyridines with butyl vinyl ether followed by acid hydrolysis of the intermediate pyridyl vinyl ether *in situ*. This method has been applied to bromoquinoline substrates as well. The reaction is compatible with a variety of functional groups.

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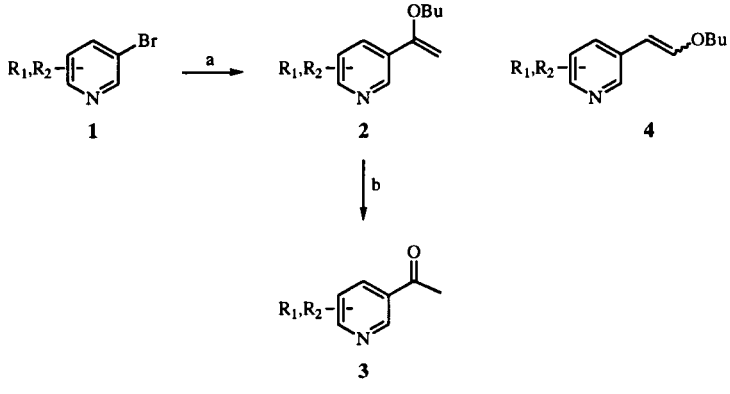
Functionalized 3-pyridyl ketones have been a relatively inaccessible class of compounds, with few synthetic approaches to functionalized 3-pyridyl ketones reported in the literature. The syntheses that have been published generally require that the corresponding pyridine 3-carboxylic acid be prepared for use as a starting material, and proceed from the pyridine 3-carboxylic acid or a derivative *via* the use of polar organometallic reagents such as organolithium or Grignard reagents [1]. Other methods that have been reported include the oxidation of indole derivatives [2], the hydration of 3-alkynyl pyridines [3], and the carbonylation of 3-bromopyridines by dicobalt octacarbonyl [4]. All of these methods have their disadvantages, including multistep reaction sequences, low overall yields, and the use of relatively inaccessible starting materials.

Scheme 1



1 2 4 3

(a) *n*-BuOCH=CH$_2$, Pd(OAc)$_2$, (*o*-tolyl)$_3$P, Et$_3$N, CH$_3$CN, 80°; (b) HCl, H$_2$O, 20°

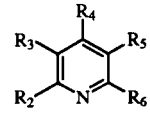
An alternative route to 3-pyridyl ketones that circumvents many of these difficulties is outlined in Scheme 1, which employs 3-bromopyridines **1** in a palladium-catalyzed Heck-type olefinic coupling with a vinyl ether [5] to afford 1-(3-pyridyl)-1-alkoxyalkenes **2**, which upon acid hydrolysis furnishes the 3-pyridyl ketones **3**. This procedure offers several advantages over those previously used for the synthesis of 3-pyridyl ketones, including mild reaction conditions that are tolerant of nearly all functional groups, a two-step, one-pot reaction, and reasonable yields. Most importantly, the necessary 3-bromopyridines are well known compounds that are readily available in good yields by a variety of methods, including functional group interchange [6], directed metalation [7], and directed electrophilic bromination of the pyridine ring [8]. In as much as Heck-type olefination reactions with vinyl ethers can afford a mixture of vinyl ether regioisomers **2** and **4**, the success of this approach depended critically upon the regiochemical outcome of the olefination reaction. However, literature precedent [9] suggested that, with an electron rich aryl bromide and the use of phosphine ligands in a coordinating solvent, the olefination should proceed with the formation of the desired vinyl ether **2** as the dominant product. Despite the fact that pyridines are generally accepted to be electron-deficient arenes, we reasoned that relatively electron-rich pyridines, such as aminopyridines and alkoxypyridines, which are sufficiently electron-rich to be capable of undergoing uncatalyzed ring halogenation, should be suitable substrates for this transformation.

In a typical experiment, the 3-bromopyridine substrate **1** was treated with 2 equivalents of butyl vinyl ether, 0.08 equivalents of palladium acetate, 0.16 equivalents of tri-*o*-tolylphosphine, and 1.6 equivalents of triethylamine in acetonitrile under reflux until the 3-bromopyridine was consumed as judged by tlc or gc analysis of the reaction

mixture. The reaction mixture was then concentrated to dryness. Analysis (gc-ms) of the crude product at this point indicated the presence of all three isomeric enol ether products: **2** and the *E*- and *Z*- isomers of **4**, with **2** being the predominant component in most cases. The residue was dissolved in 6 *M* hydrochloric acid for a short time, typically 15 minutes, which was sufficient to hydrolyse the vinyl ether intermediate **2** without effecting significant hydrolysis of the regioisomeric vinyl ether by-products 4. The product was purified by chromatography and subsequently recrystallized or distilled.

higher yield of ketone (60%). The results obtained with **1k**, **1l**, **1m**, **1n**, and **1p** suggest that the desired vinyl ether olefination reaction becomes inoperative with the most electron deficient pyridines, and that this trend can be reversed by the addition of suitable electron releasing substituents as in **1o**. Not surprisingly, 2-bromopyridines and 4-bromopyridines were unreactive under these conditions [10]. Attempts to substitute a vinyl ester for the vinyl ether component of the reaction mixture were likewise unsuccessful [11]. Tri-*o*-tolylphosphine was found to afford significantly improved yields with **1a**; by comparison, an equivalent quantity of triphenylphosphine instead of tri-*o*-tolylphosphine with **1a** under the same conditions afforded only a 41% yield of **3a**, along with much dark colored tarry material.

Table 1



Bromide	R_2	R_3	R_4	R_5	R_6	Product	R_2	R_3	R_4	R_5	R_6	Yield of 3 [a]	mp of 3, °C
1a [b]	AcNH	H	H	Br	H	**3a**	AcNH	H	H	MeCO	H	65%	146-147
1b [c]	Me_3CCONH	H	H	Br	H	**3b**	Me_3CCONH	H	H	MeCO	H	80%	113-115
1c	AcNH	H	H	Br	Me	**3c**	AcNH	H	H	MeCO	Me	96%	192-193
1d	AcNAc	Br	H	Me	H	**3d**	AcNH	MeCO	H	Me	H	52%	93-94
1e	AcNAc	Me	H	Br	H	**3e**	AcNH	Me	H	MeCO	H	40%	115-116
1f [d]	AcNH	H	Me	Br	Me	**3f**	AcNH	H	Me	MeCO	Me	90%	150-151
1g [e]	MeO	H	H	Br	H	**3g**	MeO	H	H	MeCO	H	87%	52-53
1h [f]	H	Br	H	H	H	**3h**	H	MeCO	H	H	H	70%	oil
1i [g]	-CH=CH-CH=CH-		H	Br	H	**3i**	-CH=CH-CH=CH-		H	MeCO	H	60%	94-95
1j	$C_6H_5CH_2OCONH$	H	H	Br	H	**3j**	$C_6H_5CH_2OCONH$	H	H	MeCO	H	66%	186 dec
1k	CF_3CONH	H	H	Br	H	**3k**	CF_3CONH	H	H	MeCO	H	---	no reaction
1l	TsNH	H	H	Br	H	**3l**	TsNH	H	H	MeCO	H	---	no reaction
1m	H	CO_2Et	H	Br	H	**3m**	H	CO_2Et	H	MeCO	H	13%	124-126
1n	(Succinimide)N	H	H	Br	H	**3n**	(Succinimide)N	H	H	MeCO	H	70%	137-140
1o	MeO	CO_2Et	H	Br	H	**3o**	MeO	CO_2Et	H	Br	H	60%	81-83
1p	CF_3CONMe	H	H	Br	H	**3p**	CF_3CONMe	H	H	MeCO	H	---	no reaction

[a] All yields refer to chromatographed and subsequently recrystallized or distilled products. [b] E. Placek and E. Sucharda, *Ber.*, **61**, 1813 (1928). [c] T. R. Kelly, C. T. Jagoe and Z. Gu, *Tetrahedron Letters*, **32**, 4263 (1991). [d] R. P. Mariella and E. P. Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952). [e] D. L. Comins and M. L. Killpack, *J. Org. Chem.*, **55**, 69 (1990). [f] Aldrich Chemical. [g] 3-Bromoquinoline (Aldrich Chemical).

The reaction proved to be generally successful for most of the substrate bromopyridines examined, including even such unactivated bromides such as 3-bromopyridine (Table 1). The reaction was compatible with a number of functional groups, including the amine protecting groups *N*-acetyl **1a**, *N*-pivaloyl **1b**, and *N*-benzyloxycarbonyl **1j**, as well as an ether group **1g**, and ester groups, **1m**, **1o**. The reaction was also successful for the unsubstituted pyridine **1h** and quinoline **1i**. The acyclic imides **1d** and **1e** underwent cleavage during the course of the reaction and workup to afford the amides **3d** and **3e**, while the cyclic imide **1n** survived these conditions. No reaction was observed with the trifluoroacetamides **1k** and **1p**, or the *p*-toluenesulfonamide **1l**, which were recovered unchanged in high yield. Ethyl 5-bromonicotinate (**1m**) afforded a low yield of ketone (13%), while ethyl 2-methoxy-5-bromonicotinate (**1o**) gave a four-fold

The vinyl ether intermediate **2** could be isolated from the reaction mixture if the olefination reaction mixture was concentrated and chromatographed instead of being treated with aqueous acid. Not surprisingly, the vinyl ethers **2** were extremely labile, undergoing both cleavage to the ketones **3** and polymerization.

EXPERIMENTAL

All reactions were carried under an atmosphere of dry nitrogen. All solutions were dried over anhydrous magnesium sulfate; all evaporations were carried out on a rotary evaporator at

ca. 30 Torr. Commercial reagents were used as received without additional purification. The starting materials listed in Table 1 were either known compounds or prepared by standard methods as described below. Solvents were commercial anhydrous grades and were used without further drying.

General Procedure for the Acetylation of Aminopyridines with Acetic Anhydride.

To a stirred solution of the appropriate aminopyridine (25 mmoles) in 15 ml of glacial acetic acid is added 12.8 g (125 mmoles) of acetic anhydride. The mixture is heated under reflux for 4 hours, then cooled and poured into 100 ml of water and stirred for 0.5 hour. The resulting precipitate is filtered, washed three times with water and dried.

N-(5-Bromo-6-methylpyridin-2-yl)acetamide (**1c**).

This compound was obtained in 77% yield from 2-amino-5-bromo-6-methylpyridine [12] as white flakes, mp 156-157°; ^{1}H nmr (deuteriochloroform): 8.11 (br, 1 H), 7.89 (d, 1 H), 7.74 (d, 1 H), 2.51 (s, 3 H), 2.16 (s, 3 H); ms: (NH_3 CI) m/z = 229, 231 (MH^+).

Anal. Calcd. for $C_8H_9BrN_2O$: C, 41.95; H, 3.96; N, 12.23. Found: C, 41.76; H, 4.07; N, 11.89.

N-Acetyl-*N*-(3-bromo-5-methylpyridin-2-yl)acetamide (**1d**).

This compound was obtained in 80% yield from 2-amino-3-bromo-5-methylpyridine [12] as white needles, mp 65-66°; ^{1}H nmr (deuteriochloroform): 8.34 (d, 1 H), 7.84 (d, 1 H), 2.42 (s, 3 H), 2.30 (s, 6 H); ms (NH_3 CI) m/z = 229, 231 (MH^+-AcOH).

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09; N, 10.33. Found: C, 44.28; H, 3.84; N, 10.29.

N-Acetyl-*N*-(5-bromo-3-methylpyridin-2-yl)acetamide (**1e**).

This compound was obtained in 75% yield from 2-amino-5-bromo-3-methylpyridine [12] as a white felt-like solid, mp 109-110°; ^{1}H nmr (deuteriochloroform): 8.47 (d, 1 H), 7.80 (d, 1 H), 2.25 (s, 3 H), 2.19 (s, 6 H); ms: (NH_3 CI) m/z = 229, 231 (MH^+-AcOH).

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09; N, 10.33. Found: C, 43.90; H, 3.81; N, 10.11.

(5-Bromopyridin-2-yl)carbamic Acid Benzyl Ester (**1j**).

A solution of 2-amino-5-bromopyridine [12] (6.92 g, 40 mmoles) and diisopropylethylamine (6.22 g, 48 mmoles) in 50 ml of chloroform was added dropwise to a solution of benzyl chloroformate (8.19 g, 48 mmoles) in 20 ml of chloroform at 0° with stirring. A voluminous white precipitate formed. After 15 minutes, the mixture was filtered and the precipitate was washed three times with chloroform and dried to give 2.70 g (22%) of **1j**, mp 184° dec, (2-propanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.48 (br s, 1 H), 8.37 (d, 1 H), 7.98 (dd, 1 H), 7.81 (d, 1 H), 7.40 (m, 5 H), 5.17 (s, 2 H); ms: (NH_3 CI) m/z = 307, 309 (MH^+).

Anal. Calcd. for $C_{13}H_{11}BrN_2O_2$: C, 50.84; H, 3.61; N, 9.12. Found: C, 50.57; H, 3.61; N, 8.87.

N-(5-Bromopyridin-2-yl)-2,2,2-trifluoroacetamide (**1k**).

Trifluoroacetic anhydride (1.48 ml, 10.5 mmoles) in 5 ml of tetrahydrofuran was added dropwise to a mixture of 2-amino-5-bromopyridine [12] (1.73 g, 10 mmoles) and *N,N*-diisopropylethylamine (1.83 ml, 10.5 mmoles) in 40 ml of tetrahydrofuran with stirring at 0°. After 2 hours, the mixture was evaporated and partitioned between water and ethyl acetate. The organic phase was washed with water, 1 *M* sodium bicarbonate, brine, dried, and concentrated to afford 2.61 g (97%) of **1k**, mp 73-75° (hexane-ethyl acetate); ^{1}H nmr (deuteriochloroform): 8.60 (br, 1 H), 8.39 (d, 1 H), 8.09 (d, 1 H), 7.88 (dd, 1 H); ms: (NH_3 CI) m/z = 269, 271 (MH^+).

Anal. Calcd. for $C_7H_4BrF_3N_2O$: C, 31.25; H, 1.50; N, 10.41. Found: C, 30.94; H, 1.32; N, 10.17.

N-(5-Bromopyridin-2-yl)-4-methylbenzenesulfonamide (**1l**).

p-Toluenesulfonyl chloride (5.00 g, 26 mmoles) was added to a mixture of 2-amino-5-bromopyridine [12] (4.32 g, 25 mmoles) and pyridine (2.10 ml, 26 mmoles) in 40 ml of dichloromethane and 20 ml of tetrahydrofuran. The mixture was heated in an oil bath at 60° for 18 hours, then was concentrated to dryness. The residue was stirred in water and filtered and washed with water and 1 *M* hydrochloric acid. The precipitate was dissolved in 20 ml of methanol and 15 ml of 2 *M* sodium hydroxide and stirred for 10 minutes, then acidified with 6 *M* hydrochloric acid. The precipitate was filtered, washed with water, dried, and digested with 1-propanol. The crystals were filtered and dried to afford 5.53 g (67%) of **1l**, mp 192-194° (1-propanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.50 (br, 1 H), 8.24 (m, 1 H), 7.87 (dd, 1 H), 7.75 (d, 2 H), 7.35 (d, 2 H), 6.99 (dd, 1 H), 2.32 (s, 3 H); ms: (NH_3 CI) m/z = 327, 329 (MH^+).

Anal. Calcd. for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.56. Found: C, 44.00; H, 3.51; N, 8.51.

1-(5-Bromopyridin-2-yl)pyrrolidine-2,5-dione (**1n**).

Succinic anhydride (1.12 g, 11 mmoles) was added to 2-amino-5-bromopyridine [12] (1.73 g, 10 mmoles) in 30 ml of tetrahydrofuran. The mixture was heated at reflux for 3 hours, then the solvent was evaporated and the residue was taken up in 4 ml of acetic acid and 4 ml of acetic anhydride. The mixture was heated at reflux for 2 hours and allowed to cool. The precipitated crystals were filtered, washed with ether and dried. The mother liquor was evaporated and the residue dissolved in ethyl acetate and washed with 1 *M* sodium bicarbonate, water, brine, dried and concentrated to a cystalline residue. The combined crystalline products were recrystallized from ethyl acetate to afford 1.72 g (67%) of **1n**, mp 76-78° (ethyl acetate); ^{1}H nmr (deuteriochloroform): 8.70 (d, 1 H), 7.98 (dd, 1 H), 7.21 (d, 1 H), 2.92 (s, 4 H); ms: (NH_3 CI) m/z = 255, 257 (MH^+).

Anal. Calcd. for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.37; H, 2.82; N, 10.96.

5-Bromo-2-methoxynicotinic Acid Ethyl Ester (**1o**).

A solution of 5-bromo-2-methoxynicotinic acid [13] (6.00 g, 26 mmoles) and concentrated sulfuric acid (0.8 ml, 14.4 mmoles) in 60 ml of ethanol was heated under reflux for 20 hours. The reaction mixture was allowed to cool to 20° before being treated with triethylamine (2.5 ml, 18 mmoles). The resulting precipitate was filtered, washed with water and dried to afford 5.63 g (83%) of **1o**, mp 54-55° (ethanol); ^{1}H nmr (deuteriochloroform): 8.31 (d, 1 H), 8.21 (d, 1 H), 4.34 (q, 2 H), 4.00 (s, 3 H), 1.36 (t, 3 H); ms: (NH_3 CI) m/z = 259, 261 (MH^+).

Anal. Calcd. for $C_9H_{10}BrNO_3$: C, 41.56; H, 3.88; N, 5.39. Found: C, 41.49; H, 3.86; N, 5.39.

N-Methyl-*N*-(5-bromopyridin-2-yl)-2,2,2-trifluoroacetamide (**1p**).

A solution of **1k** (3.965 g, 14.7 mmoles) in 30 ml of dry tetrahydrofuran was cooled to -60° and treated with 15.4 ml of 1 *M* sodium hexamethyldisilazide in tetrahydrofuran. After 15 minutes, the mixture was treated with iodomethane (1.1 ml, 17.7 mmoles) and dry dimethylformamide (30 ml). The cooling bath was removed and the mixture was stirred at 20° for 24 hours. The reaction mixture was then evaporated in high vacuum, and the residue partitioned between water and ethyl acetate. The organic extract was washed with water, sodium bicarbonate, and brine, dried, and evaporated. The residue was recrstallized twice to afford 1.77 g (42%) of **1p** as colorless crystals, mp 148-149° (hexanes-ethyl acetate); ^{1}H nmr (deuteriochloroform): 8.39 (d, 1 H), 7.85 (d, 1 H), 7.77 (dd, 1 H), 3.90 (s, 3 H); ms: (NH_3 CI) m/z = 283, 285 (MH^+).

Anal. Calcd. for $C_8H_6BrF_3N_2O$: C, 33.95; H, 2.14; N, 9.90. Found: C, 34.00; H, 1.91; N, 9.72.

General Procedure for the Reaction of Heteroaryl Bromides **1** with Butyl Vinyl Ether.

A mixture of the bromide **1** (5 mmoles), butyl vinyl ether (1.00 g, 10 mmoles), tri-*o*-tolylphosphine (0.245 g, 0.8 mmole), palladium acetate (0.090 g, 0.4 mmole), and triethylamine (1.10 ml, 7.9 mmoles) in 10 ml of acetonitrile containing 15 mg of hydroquinone is heated under reflux for 18 hours. The reaction mixture is then cooled, concentrated, and the residue is taken up in 10 ml of 6 *M* hydrochloric acid and stirred for 15 minutes. The mixture is then diluted with 40 ml of ethyl acetate, adjusted to *p*H = 8 with 6 *M* sodium hydroxide, and the aqueous phase is saturated with sodium chloride. The ethyl acetate layer is separated, dried, and concentrated. The residue is chromatographed on silica gel to afford the product ketone, which is subsequently recrystallized or distilled as appropriate.

N-(5-Acetylpyridin-2-yl)acetamide (**3a**).

This compound was obtained in 65% yield from **1a** as white needles after chromatography (2:1 ethyl acetate-hexanes), mp 146-147° (1:4 ethanol-hexanes); ^{1}H nmr (deuteriochloroform): 8.82 (br s, 1 H), 8.21 (m, 3 H), 2.56 (s, 3 H), 2.22 (s, 3 H); ms: (NH_3 CI) m/z = 179 (MH^+).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.37; H, 5.62; N, 15.81.

N-(5-Acetylpyridin-2-yl)-2,2-dimethylpropionamide (**3b**).

This compound was obtained in 80% yield from **1b** as white rhombs after recrystallization of the crude product without chromatography, mp 113-115° (2-propanol); ^{1}H nmr (deuteriochloroform): 8.84 (d, 1 H), 8.32 (d, 1 H), 8.23 (d, of d, 1 H), 8.20 (br, 1 H), 2.59 (s, 3 H), 1.34 (s, 9 H); ms: (NH_3 CI) m/z = 221 (MH^+).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.17; H, 7.27; N, 12.73.

N-(5-Acetyl-6-methylpyridin-2-yl)acetamide (**3c**).

This compound was obtained in 96% yield from **1c** as white flakes after chromatography (2:1 hexanes-ethyl acetate), mp 201-202° (2-propanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): 8.27 (d, 1 H), 8.01 (d, 1 H), 2.59 (s, 3 H), 2.53 (s, 3 H), 2.11 (s, 3 H); ms: (NH_3 CI) m/z = 193 (MH^+).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.46; H, 6.11; N, 14.55.

N-(3-Acetyl-5-methylpyridin-2-yl)acetamide (**3d**).

This compound was obtained in 52% yield from **1d** as a white solid after chromatography (2:1 ethyl acetate-hexanes), mp 99-100° (2-propanol); ^{1}H nmr (deuteriochloroform): 11.08 (br, 1 H), 8.41 (d, 1 H), 7.94 (d, 1 H), 2.63 (s, 3 H), 2.35 (s, 3 H), 2.34 (s, 3H); ms: (NH_3 CI) m/z = 193 (MH^+).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.31; N, 14.53.

N-(5-Acetyl-3-methylpyridin-2-yl)acetamide (**3e**).

This compound was obtained in 40% yield from **1e** as a white solid after chromatography (2:1 ethyl acetate-hexanes), mp 115-116° (ethyl acetate); ^{1}H nmr (deuteriochloroform): 8.26 (d, 1 H), 7.79 (br, 1 H), 7.68 (d, 1 H), 2.24 (s, 9 H); ms: (NH_3 CI) m/z = 193 (MH^+).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.84; H, 6.43; N, 14.19.

N-(5-Acetyl-4,6-dimethylpyridin-2-yl)acetamide (**3f**).

This compound was obtained in 90% yield from **1f** as white needles after chromatography (2:1 hexanes-ethyl acetate), mp 150-151° (ethyl acetate); ^{1}H nmr (deuteriochloroform): 7.86 (s, 1 H), 7.77 (br, 1 H), 2.47 (s, 3 H), 2.33 (s, 3 H), 2.25 (s, 3 H), 2.16 (s, 3 H); ms: (NH_3 CI) m/z = 207 (MH^+).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.10; H, 6.98; N, 13.35.

1-(6-Methoxypyridin-3-yl)ethanone (**3g**).

This compound was obtained in 87% yield from **1** as colorless crystals after chromatography (2:1 ethyl acetate-hexanes), mp 52-53° (cyclohexane); ^{1}H nmr (deuteriochloroform): 8.77 (d, 1 H), 8.14 (dd, 1 H), 6.78 (d, 1 H), 4.00 (s, 3 H), 2.56 (s, 3 H); ms: (NH_3 CI) m/z = 152 (MH^+).

Anal. Calcd. for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.60; H, 6.06; N, 9.07.

3-Acetylpyridine (**3h**).

This compound was obtained in 70% yield from **1h** as a colorless oil after chromatography (2:1 ethyl acetate-hexanes) and Kugelrohr distillation. The ^{1}H nmr (deuteriochloroform), mass spectrum, and gc were identical with that of a commercial authentic sample (Aldrich).

3-Acetylquinoline (**3i**).

This compound was obtained in 60% yield from **1i** as colorless needles after chromatography (2:1 ethyl acetate-hexanes), mp 94-95° (hexanes); lit 92-93° [14].

(5-Acetylpyridin-2-yl)-carbamic Acid Benzyl Ester (**3j**).

This compound was obtained in 66% yield from **1j** as white needles after recrystallization of the crude product without chromatography, mp 186 dec, (ethyl acetate); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.76 (br s, 1 H), 8.85 (d, 1 H), 8.25 (dd, 1 H), 7.96 (d, 1 H), 7.41 (m, 5 H), 5.19 (s, 2 H), 2.54 (s, 3 H); ms: (NH_3 CI) m/z = 271 (MH^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.29; H, 4.89; N, 10.30.

5-Acetylnicotinic Acid Ethyl Ester (**3m**).

This compound was obtained in 13% yield from **1m** after chromatography (23:2 dichloromethane-ethyl acetate) as colorless crystals, mp 124-126° (ethanol); lit mp 124-125° [15].

1-(5-Acetylpyridin-2-yl)pyrrolidine-2,5-dione (**3n**).

This compound was obtained in 70% yield from **1n** after chromatography (24:1 dichloromethane-methanol) as a colorless oil that crystallized on standing, mp 137-140° (ethyl acetate); ^{1}H nmr (deuteriochloroform): 9.17 (d, 1 H), 8.39 (dd, 1 H), 7.44 (d, 1 H), 2.94 (s, 4 H), 2.65 (s, 3 H); ms: (NH_3 CI) m/z = 219 (MH^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62. Found: C, 60.46; H, 4.78.

5-Acetyl-2-methoxynicotinic Acid Ethyl Ester (**3o**).

This compound was obtained in 60% yield from **1o** after chromatography (22:3 dichloromethane-ethyl acetate) as colorless crystals, mp 81-83° (hexanes-ethyl acetate); ^{1}H nmr (deuteriochloroform): 8.87 (d, 1 H), 8.65 (d, 1 H), 4.38 (q, 2 H), 4.10 (s, 3 H), 2.58 (s, 3 H), 1.38 (t, 3 H); ms: (NH_3 CI) m/z = 224 (MH^+).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.24; H, 5.86; N 6.33.

Isolation of the Intermediate Vinyl Ether **2**.

N-[5-(1-Butoxyvinyl)pyridin-2-yl]acetamide (**2a**).

A mixture of **1a** (1.07 g, 5 mmoles), butyl vinyl ether (1.00 g, 10 mmoles), tri-*o*-tolylphosphine (0.245 g, 0.8 mmole), palladium acetate (0.090 g, 0.4 mmole), and triethylamine (1.10 ml, 7.9 mmoles) in 10 ml of acetonitrile containing 15 mg of hydroquinone was heated under reflux for 18 hours. The reaction mixture was then cooled, concentrated, and the residue was taken up in ether and water. The ether phase was separated, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (6:1 benzene-ethyl acetate) as rapidly as possible to afford 0.254 g of **2a** as a colorless oil that rapidly crystallized, mp 55-58° (hexane); ^{1}H nmr (deuteriochloroform): δ = 8.48 (m, 1 H), 8.42 (br s, 1 H), 8.24 (m, 1 H), 7.93 (m, 1 H), 4.60 (d, 1 H), 4.23 (d, 1 H), 3.84 (t, 3 H), 2.21 (s, 3 H), 1.77 (m, 2 H), 1.48 (m, 2 H), 0.97 (t, 3 H); ms: (EI) m/z = 234 (M^+).

REFERENCES AND NOTES

[1] W. Korytnyk, A. C. Ghosh, N. Angelino and C. Dave, *J. Med. Chem.*, **16**, 959 (1973); C. M. Atkinson and B. N. Biddle, *J. Chem. Soc. (C)*, 2053 (1966); T. Gungor, F. Marsais and G. Queguiner, *J. Organomet. Chem.*, **215**, 139 (1981); J. T. Edward and L. Y-S. Mo, *J. Heterocyclic Chem.*, **10**, 1047 (1973); G. H. Cooper and R. L. Rickard, *J. Chem. Soc.*, 772 (1971).

[2] B. A. J. Clark and J. Parrick, *Tetrahedron*, **30**, 475 (1974).

[3] T. Sakamoto, Y. Kondo, M. Shiraiwa and H. Yamanaka, *Synthesis*, 245 (1984).

[4] M. Miura, F. Akase and M. Nomura, *J. Chem. Soc., Chem. Commun.*, 241 (1986).

[5] G. D. Daves, Jr. and A. Hallberg, *Chem. Revs.*, **89**, 1433 (1989).

[6] J. P. Schaeffer, J. Higgins and P. K. Shenoy in H. E. Baumgarten, Org. Synth., Coll. Vol. V, Wiley, New York, NY, 1973, p 142.

[7] J. A. Turner, *J. Org. Chem.*, **48**, 3401 (1983).

[8] B. A. Fox and T. L. Threlfall in H. E. Baumgarten, Org. Synth., Coll. Vol. V, Wiley, New York, NY, 1973, p 346.

[9] A. Hallberg, L. Westfelt and B. Holm, *J. Org. Chem.*, **46**, 5414 (1981); C-M. Andersson and A. Hallberg, *J. Org. Chem.*, **52**, 3529 (1987); I. Kuwajima and H. Urabe, *J. Am. Chem. Soc.*, **104**, 6831 (1982). The separation of the product mixture resulting from the presence of **2** and **4** is simplified by the obsevation of Hallberg that vinyl ethers **2** undergo acid-catalyzed hydrolysis at a much faster rate than do vinyl ethers **4**.

[10] Very low yields (<10%) of products were obtained with 2-bromopyridine, 4-bromopyridine, and 2-bromo-6-methoxypyridine. See R. F. Heck in Organic Reactions, Vol **27**, Wiley, New York, NY, 1982, p 345.

[11] No product **3a** formation was observed (gc analysis) in the reaction of **1a** with either vinyl acetate or vinyl butyrate. Vinyl esters are known to be generally poor substrates for Heck-type olefination reactions; see [10].

[12] This compound was purchased from Lancaster Synthesis.

[13] R. Sarges, S. W. Goldstein, M. Welch, A. C. Swindell, T. W. Siegel, and T. A. Beyer, *J. Med. Chem.*, **33**, 1859 (1990) and references cited therein.

[14] A. Stener, *Gazz. Chim. Ital.*, **90**, 1365 (1960).

[15] R. Lukes and P. Vaculik, *Collect Czech. Chem. Commun.*, **23**, 954 (1958).